2013 PDA/FDA Improving Investigations Workshop – Output of Meeting

The ICH Q10 Workshop Series: The Practical Approach to Sustainable Compliance

September 18-19, 2013 - Washington, DC

Need for Proper Investigations

Inadequate investigations remain one of industry's top five inspectional findings by FDA in domestic and foreign pharmaceutical company inspections.

- Consistent with inspectional findings from many other health authorities around the world

Examples:

- Lack of adequate detail
- Scope not broad enough
- Inadequate rationale for batch disposition
- Lack of root cause analysis
- Failure to address issues at CMOs
- Complaints not substantially investigated or trends not detected

Presentation Overview


Expectations of a Well-Executed Investigation


Staffing and Scoping an Investigation


Executing an Investigation


Corporate Control and Vigilance


Assuring Effectiveness of Corrective Actions

Investigation Expectations

Investigations: FDA Expectations and Findings

- …Clearly the responsibility for maintaining quality rests squarely with the manufacturers themselves…the widespread and **successful adoption of six sigma and related quality management techniques** in other manufacturing sectors would imply that **reliable, high-quality manufacturing** is also attainable in the pharmaceutical sector.

- We must ask ourselves, in an area where the stakes are so high, why is this not being achieved?

Dr. Janet Woodcock, Commentary in May-June 2012 edition of PDA Journal

Richard L. Friedman, M.S. Associate Director, OMPQ, Office of Compliance, US FDA
PDA / FDA Improving Investigations Workshop, September 18, 2013

Preventing Adverse Quality Impact

Identify Signals	• Identify internal signal (QC/QA) before there is a drug quality consequence • Monitor external (voice of customer) signals, especially complaints
Prevention	• Implement upstream process controls, robust statistical sampling plans, operational supervision, and recording of anomalies as deviation • Such a quality culture will identify problems during process, before final QC stage
When a meaningful manufacturing issue is emerging/occurring	• Know when Management Escalation is needed→ ensure timely communication • Prevention/Correction may require obtaining resources for root cause determinations and reinvestment in facilities
Use the CAPA Program Effectively	• Catch leading indicators of quality problems internally and deal with them early on to help avoid external failures (e.g., complaints, FARS/BPDR, recalls)

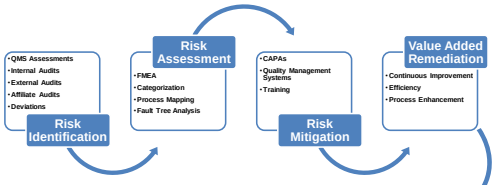
Richard L. Friedman, M.S. Associate Director, OMPQ, Office of Compliance, US FDA
PDA / FDA Improving Investigations Workshop, September 18, 2013

To Maintain a State of Control…

Science-based management of quality includes **monitoring ongoing process control,** and **acting promptly to effectively address risks before the process falls out of a state of control.**

Richard L. Friedman, M.S. Associate Director, OMPQ, Office of Compliance, US FDA
PDA / FDA Improving Investigations Workshop, September 18, 2013

Benefits and Elements of Establishing an Robust Investigation Process

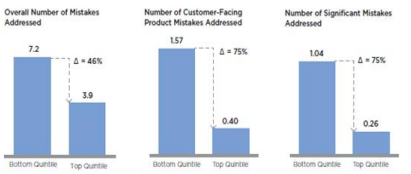


The aim is to elevate compliance beyond execution to a strategic framework that integrates business processes with compliance requirements based on risk based solutions that are efficient, effective and innovative.

Juan L. Torres, PhD, SVP, Global Quality - Biogen Idec, PDA / FDA Improving Investigations Workshop, September 18, 2013

Process Improvement = Overall Benefit

Culture's Impact on Mistakes Addressed by Employees
Weekly Average per Employee



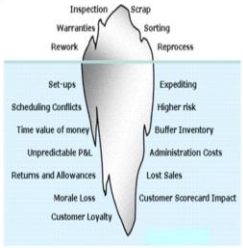
Based on CEB large-scale survey of over 850 employees across levels of seniority, functions, and industries to understand the nature and drivers of quality in a company's culture.

A $350 Million Opportunity

Moving from the bottom 20% to the top 20% in Culture of Quality Index performance can lead to more than **$350 million in added employee productivity.**[1]

Juan L. Torres, PhD, SVP, Global Quality - Biogen Idec, PDA / FDA Improving Investigations Workshop, September 18, 2013

Cost of Quality: models and the benefits



- Reducing the cost of poor quality is one of the best ways to increase a company's profit
- Provides management overview of quality
- Aligns quality and goals
- Helps prioritize problems and provides a means to measure process improvements
- Provides a means to distribute controllable quality costs
- Promotes effective use of resources
- Provides incentives for robust Quality

Juan L. Torres, PhD, SVP, Global Quality - Biogen Idec, PDA / FDA Improving Investigations Workshop, September 18, 2013

Management Review and Responsibility for Investigations

- Be proactive
- Address issues promptly
- Foster a continuous improvement environment
- Create management ownership
- Allocate resources adequately and appropriately
- Drive "Right the First Time" approaches
- Promote leadership and decision making across levels and functions
- Be persistent and tenacious

Martin VanTrieste, R.Ph. SVP Quality, Amgen, Inc.
PDA / FDA Improving Investigations Workshop
September 18, 2013

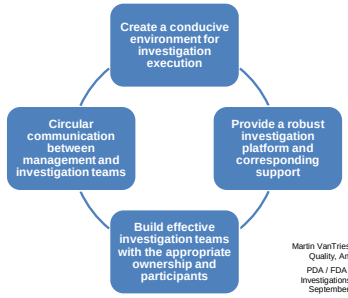
Standardized Root Cause Analysis (SRCA) Process Improves CAPAs

SRCA Process avoids "tunnel vision" by:

- Emphasizing that most events have multiple Causal Factors and Root Causes
- Requiring evaluation of Causal Factors and Root Causes
- Requiring confirmation of Causal Factors
- Evaluating each Causal Factor for Root Cause(s)
- Ensuring CAPAs are implemented for each identified Root Cause

Martin VanTrieste, R.Ph. SVP Quality, Amgen, Inc. PDA / FDA Improving Investigations Workshop
September 18, 2013

Successful Investigations are Critical to the Health of Our Business



Martin VanTrieste, R.Ph. SVP Quality, Amgen, Inc.
PDA / FDA Improving Investigations Workshop
September 18, 2013

Staffing and Scoping an Investigation

Forming an Investigation Team

General Considerations for Investigation Team Establishment

Product Type	Product Ownership	External to Site
• Sterile/Injectable • Biologic/Vaccine • Inhalation	• CMO • Joint Venture	• Supply chain internal/external • Other Sites • Material Supplier • Equipment Vendor • Service Provider

Swroop Sahota, PhD, VP Quality Operations – Catalent, PDA / FDA Improving Investigations Workshop
September 18, 2013

Engaging the Right People

Subject Matter Experts
- Method Development
- Microbiology
- Formulation Development
- Technical Operations
- Validation
- Supplier

Investigation Team Leader
- Site Quality Head
- Site Operations Head
- Global QA
- Global Technical Operations

Management Sponsor
- Matrixed organization
- Complex Issues

Swroop Sahota, PhD, VP Quality Operations - Catalent
PDA / FDA Improving Investigations Workshop
September 18, 2013

Key Staffing and Scoping Concepts

Involving the right people is key
- Get to Root Cause
- Timely closure
- Manage impact and communication

One size doesn't fit all

Apply product, technology, supply chain and other external considerations when selecting a team

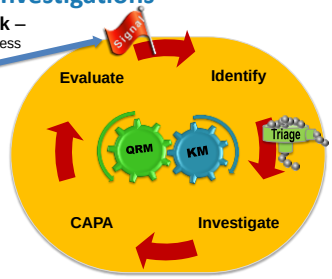
Get management sponsorship!

Swroop Sahota, PhD, VP Quality Operations - Catalent
PDA / FDA Improving Investigations Workshop
September 18, 2013

Deviations, Complaints, QC Failures, and other Investigations

How to Gauge Risk –
Importance of Triage process

- Complaints
- Product Rejections
- Non-Conformances
- Recalls
- Deviations
- Audits
- Regulatory Inspections and Findings
- Trends from Process Performance & Product Quality Monitoring

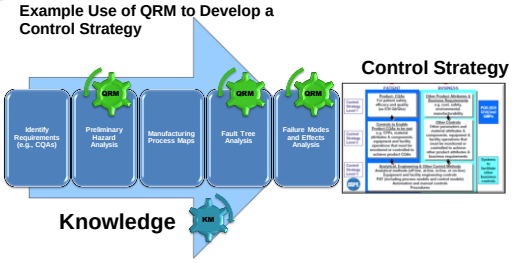


QRM and Knowledge Management serve as enablers to improve the efficiency and effectiveness of the Triage step and of the overall CAPA System.

Jacques Zimmowitch, Vice President Quality - Drug Product Operations, Americas and Asia - Eli Lilly and Company
PDA / FDA Improving Investigations Workshop, September 18, 2013

QRM and KM to Assess Risks and Support Triage Process

Example Use of QRM to Develop a Control Strategy



Jacques Zimmowitch, Vice President Quality - Drug Product Operations, Americas and Asia - Eli Lilly and Company
PDA / FDA Improving Investigations Workshop, September 18, 2013

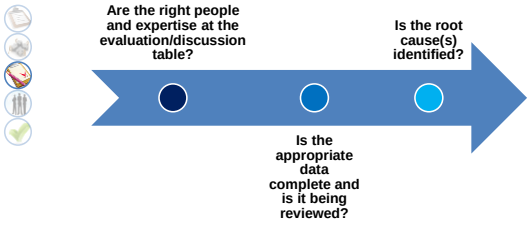
Key concepts in this presentation

Investigations and CAPA	• Key Continuous Improvement Tools • Ultimately Supports Operational Excellence
Triage	• Use Risk Assessment and Knowledge Management to focus resources and ensure Patient Safety
Timing	• Triage and investigate quickly, to control the problem, to collect and apply process knowledge and to escalate as required
Scope	• Control the impacted batches, but also consider what other products, materials, equipment or even other manufacturing sites could be impacted now or in the future

Jacques Zimmowitch, Vice President Quality - Drug Product Operations, Americas and Asia - Eli Lilly and Company
PDA / FDA Improving Investigations Workshop, September 18, 2013

Executing an Investigation

Essential Components for a Thorough Investigation



Thomas Arista, National Expert Investigator - ORA, FDA
PDA / FDA Improving Investigations Workshop, September 18, 2013

Notification Evaluation

Is it major, minor or can it wait?

Is this a deviation(s) and does it impact:

- Due to product quality related complaints;
- Issues related to non-sterile products;
- Aseptic operations and/or due to media fill failures;
- Microbial and/or non-viable particles contamination; and,
- Are these reoccurring aberrant events?

Thomas Arista, National Expert Investigator - ORA, FDA
PDA / FDA Improving Investigations Workshop, September 18, 2013

Essential Quality Unit Personnel

Shop Floor Operations

- Manufacturing/production
- Engineering
- I.T. staff
- Maintenance
- Laboratory Analysts

First Line Supervisor/ Team Leader

Manager/Director

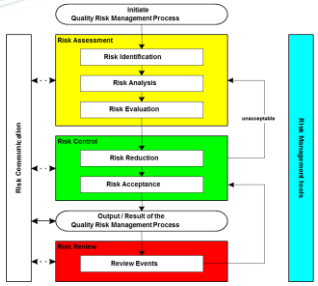
Sr. VP/Ex. VP/VP

Pres./CFO/COO

CEO

Thomas Arista, National Expert Investigator - ORA,FDA
PDA / FDA Improving Investigations Workshop, September 18, 2013

Getting to the Root Cause



Shane Ernst, VP Quality, Hospira
PDA / FDA Improving Investigations Workshop, September 18, 2013

Getting to the Root Cause

Risk is never zero
- It is mitigated or reduced to an acceptable level.

Uncertainty is caused by having little or no data
- Beware of performing risk assessments with high uncertainty

Documentation and communication of risk is critical

Risk management and the associated tools
- Allow a sound decision to be made…
- …NOT to justify it

Shane Ernst, VP Quality, Hospira
PDA / FDA Improving Investigations Workshop, September 18, 2013

Root Cause Analysis (RCA) Tools

Risk Management Tool	Process Mapping	Potential Cause Identification	Root Cause Analysis	Impact Assessment	CAPA Assessment
Flowcharts	X				
Check Sheets	X	X		X	X
Process Mapping	X				
Cause & Effect Diagram		X			
FMEA/FMECA			X	X	X
HACCP					X
HAZOP			X		
PHA			X	X	
Risk Ranking & Filtering				X	X
Statistical Tools		X	X	X	X

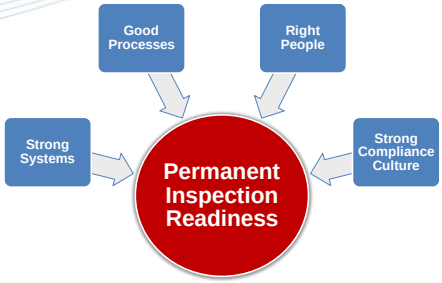
Shane Ernst, VP Quality, Hospira
PDA / FDA Improving Investigations Workshop, September 18, 2013

Corporate Control and Vigilance

Investigation Input Triggers
- PPPQMS
- Management Review
- CAPA

Investigation Level
- Comprehensive
- Less intense

Corporate Control and Vigilance



Lori F. Hirsch, Managing Counsel - Merck
PDA / FDA Improving Investigations Workshop, September 18, 2013

Benefits of Robust Proactive Compliance

- Support and ownership of quality goes beyond quality/compliance units
- Enhanced process stability drives productivity and performance
- Prevention reduces compliance risks and costs
- Fewer significant investigations and therefore, more efficient release of product
- Protection of the product brand and reputation

Lori F. Hirsch, Managing Counsel - Merck
PDA / FDA Improving Investigations Workshop, September 18, 2013

Quality Lessons

Deviations occur/mistakes happen!

Key is to have systems in place that:

- Provide for strict accountability/checks and balances
- Investigate root causes
- Assure complete and systemic CAPAs
- Check effectiveness

Apply "Lessons Learned" across product lines, sites and throughout the organization

Lori F. Hirsch, Managing Counsel - Merck
PDA / FDA Improving Investigations Workshop, September 18, 2013

Handling Customer Complaints

Transition via a Phased Quality Strategy

GOAL
Quality Excellence

World -class leader that anticipates and responds to evolving patient, regulatory and customer needs which contributes to the continuous success of Hospira

APPLICATION
Deployment of Enhanced Process with Emphasis and Commitment to Public Health and Patient Safety

1. Implementation of metrics for quantitative feedback
2. Constant management oversight and monitoring of metrics
3. Reactive and proactive response to metrics

CHANGE
Enhance Complaint Processes and Supporting Systems

1. Unifying process across Hospira globally
2. Improved process and procedural cohesion
3. Global implementation

FOUNDATION
Change the Mindset and Improve culture

1. Develop Talent Management for Quality-Minded People
2. Build the Quality Minded Compliance Team
3. Harmonize experience through Communities of Practice

Meera Khullar, Lead Dir. Pharmaceutical Qual. Operations – Hospira
PDA / FDA Improving Investigations Workshop, September 18, 2013

Quality Lessons

- **Global process helped in driving consistency across sites**
- **Enhancement of other supporting processes (e.g. Notification to Management, FAR)**
- **Complaint management review served as a common learning platform and launch of global initiatives**
- **Enhancements to the process leads to customer centricity**
- **Positive impact on complaint reduction and cycle time; thereby improving and ensuring patient safety**

Meera Khullar, Lead Dir. Pharmaceutical Qual. Operations – Hospira
PDA / FDA Improving Investigations Workshop, September 18, 2013

Quality Lessons

Meera Khullar, Lead Dir. Pharmaceutical Qual. Operations – Hospira
PDA / FDA Improving Investigations Workshop, September 18, 2013

Assuring Effectiveness of Corrective Actions

Preventing Repeat Issues

- Effective CAPA
- Continual improvement

Assessing CAPAs

- Long-term efficacy
- Monitor post-implementation

Identifying the Right Corrective Actions

Control
- Standardize and document
- Control Charts
- Evaluating results

Improve
- Generate and select solutions
- Pilot and implement solutions

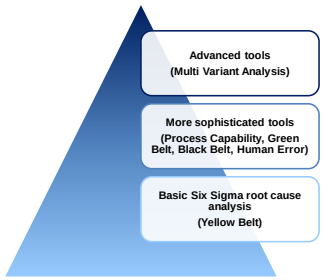
Define
- Problem Definition
- Process Mapping

Measure
- Gather and Display data
- Time Series Plot
- Pareto Chart

Analyze
- Process Analysis
- Brainstorming
- Analyze Cause & Effect

Sharon Timmis, VP Operational Excellence - Pfizer Global Supply
PDA / FDA Improving Investigations Workshop, September 18, 2013

Applying Corrective Action Tools



Sharon Timmis, VP Operational Excellence - Pfizer Global Supply
PDA / FDA Improving Investigations Workshop, September 18, 2013

Applying Corrective Action Tools - Example

Task Required	Who does it?	By when?	Frequency?	Comments
Investigations & Event Control charts updated weekly	QA-rep	2nd Nov	Weekly	Use I-MR chart.
If Outliers on Control chart or Investigations/ Events take >28d, these must be investigated (in real-time) at the board	Board Facilitator to nominate investigator	Investigation to be completed within 1 week	As required	Outliers are Special Causes where the data point is > 3 std-devs away from the average.
Shifts, Trends and Sawtooth patterns in the Control Charts to be discussed / investigation initiated at the monthly CI meeting	Board Facilitator and CI team	Investigation to be completed within 1 week	As required	Shift is 8 points in a row above or below the average. Trend is 6 points in a row increasing or decreasing. Saw tooth is 14 points in a row alternating up and down.
Set up monthly CI meetings	Board Facilitator	2nd Nov	Monthly	This is a key element to ensure gains are maintained and that ongoing CI of the system occurs.

Sharon Timmis, VP Operational Excellence - Pfizer Global Supply
PDA / FDA Improving Investigations Workshop, September 18, 2013

Assuring Effective Corrective Actions

- Understanding Root Cause
- Establishing Corrective/Preventive Actions
- Assuring CAPA Effectiveness
- Management responsibility
- Example of CAPA Effectiveness

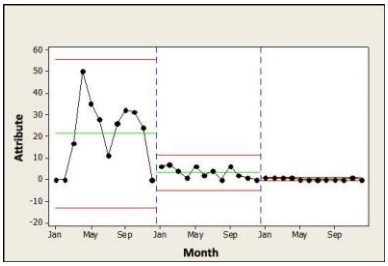
Veronica Cruz, PhD - VP, Q&C - Johnson & Johnson
PDA / FDA Improving Investigations Workshop, September 18, 2013

Corporate Control and Vigilance

Understanding Root Cause	• Investigate to develop knowledge, not to release the batch
Establishing Corrective/Preventive Actions	• Correct the event, avoid reoccurrence, prevent similar events in other areas
Assuring CAPA Effectiveness	• Effective CAPA reduce and control process variation
Management responsibility	• Periodic Quality Systems Review

Corporate Control and Vigilance

Monitoring CAPA Effectiveness



Workshop Summary

Have the right Team
- Team composition can change when new knowledge is discovered

Be open minded
- Do not go straight to solutions without looking at all relevant data

Senior management and health authority involvement
- Notification processes in terms of timing and level of detail provided

Compiled by Anders Vinther and Jen Magnani, Genentech
PDA / FDA Improving Investigations Workshop, September 18, 2013

Participant Feedback

Successfully concluding an investigation is dependent on:	• Effectively getting to the root cause • Effective CAPAs to prevent repeat deviation • Effectiveness monitoring ensure the CAPA is correct
Internal company communication with emphasis on:	• Importance of sharing and documenting knowledge gained and lessons learned • Sharing the information efficiently through the quality system
Participant face-to-face discussions showed:	• Most investigations have similar elements that need to be covered • There are many ways of conducting a thorough investigation
Each attendee received:	• All case study materials • Summary of the lessons learned (generated by all the attendees) • Example of a detailed Points to Consider list for conducting investigations • A simple root cause analysis tool guide

Compiled by Anders Vinther and Jen Magnani, Genentech, PDA / FDA Improving Investigations Workshop, September 18, 2013

Acknowledgements

- Josh Eaton (PDA S&RA)
- Veronica Cruz, PhD (Johnson & Johnson)
- Joyce Bloomfield (Merck)
- Gabriele Gori (Norvartis, PDA BOD)
- Steve Mendevil (Amgen, PDA BOD)
- Marty Nealey (Hospira)
- Anil Sawant (J&J, PDA's RAQAB)
- Sue Schniepp (Allergy Labs, PDA BOD)
- Jen Magnani, Genentech/Roche
- Sharon Timmis, Pfizer Global Supply
- Anders Vinther (Genentech /Roche
- Glenn Wright (Eli Lilly, PDA BOD)